Report

October 2014

Ontario

Health Quality Ontario

Qualité des services
de santé Ontario

The Accuracy of Fine-Needle Aspiration Cytology in the Diagnosis of Lymphoma

Health Quality Ontario

Context

The gold standard method of diagnosing and subclassifying lymph node lesions is to do a histopathological analysis of tissue removed by excisional biopsy. However, this requires local or general anesthesia and may be associated with complications. Using fine-needle aspiration to collect a sample for cytological examination is less invasive and can be done more rapidly.

Research Question

What is the accuracy of fine-needle aspiration cytology in the diagnosis of lymphoma?

Conclusion

Fine-needle aspiration cytology alone may not be appropriate in the diagnosis and subclassification of lymphoma, and its use may be associated with a delay in obtaining a definitive diagnosis.

Methodology

Research questions are developed by Choosing Wisely Canada, in consultation with experts, end users, and/or applicants in the topic area. Evidence Development and Standards then produces one of two types of rapid reviews, or a special report to answer the research question. A rapid review of Systematic Reviews is conducted when a systematic literature search identifies relevant systematic reviews, health technology assessments, or meta-analyses that meet the inclusion criteria specified in the methods section. A rapid review of primary studies is conducted when none of the aforementioned study designs are available. On occasion, a special report may be provided that does not strictly follow the rapid review methodology set out by HQO. These reports are completed in a 2- to 8-week time frame. For more detail on rapid review methodology, please visit the Health Quality Ontario website at: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/rapid-reviews

Context

Objective of Review

The objective was to evaluate the accuracy of fine-needle aspiration cytology in the diagnosis of lymphoma.

Clinical Need and Target Population

Description of Disease/Condition

Lymphadenopathy is a condition in which lymph nodes are abnormal in size, consistency, or number. (1) A common presentation in most clinics and hospitals, (1, 2) it can be caused either by benign conditions such as inflammation or by malignant conditions such as metastatic tumours or lymphomas. (1, 3)

The gold standard method for diagnosing and subclassifying lymph node lesions is to do a histopathological analysis on excisional node biopsy, i.e., a histopathological analysis of tissue removed by excision. (2) However, the excisional biopsy requires general or local anesthesia and may be associated with complications. (2, 4)

Lymphoma classification systems commonly used, such as the World Health Organization (WHO) system and the Revised European-American Classification of Lymphoid Neoplasms (REAL), are based on morphology, immunology, and cytogenetic changes. (2)

Technology/Technique

Fine-needle aspiration (FNA) cytology uses a narrow-gauge needle (22- to 25-gauge) and a plastic syringe to collect a sample for cytological examination. (5, 6) Two advantages of FNA are that it is less invasive and more rapid than excisional biopsy. (1, 7) Possible limitations include loss of cell architecture, which makes subclassification of lymphoma more difficult, (4, 8) sampling error, and aspiration of inadequate material. (8) Ancillary techniques such as flow cytometry or immunophenotyping/immunocytochemistry may improve the accuracy of FNA cytology. (8, 9)

Question, Methods, and Findings

Research Question

What is the accuracy of fine-needle aspiration cytology in the diagnosis of lymphoma?

Methods

See Appendix 1 for a detailed description of the search strategy, including terms and results.

Inclusion Criteria

- English-language full-text publications
- published between January 1, 2004, and May 28, 2014
- observational studies, randomized controlled trials (RCTs), systematic reviews, and meta-analyses
- studies evaluating the accuracy of fine-needle aspiration (FNA) cytology in the diagnosis of lymphoma, using histopathologic analysis on excisional biopsy as the gold standard
- studies including mostly adult patients with suspected lymphoma

Exclusion Criteria

- < 20 patients included
- studies where the gold standard was not used on all included patients
- studies restricted to cases where the decision to perform excisional biopsy was based on FNA cytology results

Outcomes of Interest

- sensitivity (true positives/[all those with the disease])
- specificity (true negatives/[all those without the disease])
- length of time from the first FNA cytology until diagnosis of lymphoma by excisional biopsy

Findings

The database search yielded 929 citations published between January 1, 2004, and May 28, 2014 (duplicates removed). Articles were then excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

Nine observational studies met the inclusion criteria. (1, 2, 4, 7-9, 13-15) The reference lists of the included studies were hand-searched to identify other relevant studies, but no additional citations were identified.

Three studies were prospective (2, 9, 15) while the remaining 6 studies were retrospective. Patients in the retrospective studies received FNA cytology for the diagnosis of lymphoma in addition to the gold standard (excisional biopsy of lymph nodes), i.e., patients who underwent FNA cytology alone were

excluded from these studies as they had not received the gold standard. The prospective studies included consecutive patients with suspected lymphoma who received both FNA and excisional biopsy. The FNA procedure was not described in detail in most studies and the excisional biopsy procedure was not described in any of the studies (see Table 1).

Four studies reported using the REAL or WHO lymphoma classification systems. (8, 9, 13, 14) No information was provided on this in the remaining studies. Most studies did not report the time interval between the FNA cytology and the excisional biopsy procedures. Table 1 provides additional details about the studies included.

Four studies included only patients with cervical or head and neck lymphoma (4, 7, 14, 15) and 1 study included only patients with thyroid lymphoma. (13) Tables 1 and 2 provide more details about patient characteristics.

Khillan et al (7) reported that 8 patients (28.6%) required a second FNA procedure because the initial procedure was not diagnostic, and that 1 patient (3.6%) required a third FNA procedure. Another study (8) reported that a second FNA procedure was required in most patients included, without providing details on the reasons for the second procedure.

Sensitivity and Specificity

Seven studies reported on the sensitivity of FNA cytology, using excisional biopsy as the gold standard. (1, 2, 4, 7, 9, 13, 14)

The sensitivity of FNA cytology (percentage of cases correctly identified as lymphoma by FNA [true positives] among all lymphoma cases identified by excisional biopsy in the study) ranged from 25% to 95%. It is unclear what could have accounted for this wide variation, though it may be partially due to how the studies defined the true positive cases. Some studies considered an FNA cytology diagnosis suggestive of lymphoma as a true positive, while others considered that as a negative result. For instance in the study by Seningen et al (13), if the cases identified by FNA cytology as atypical or suspicious were considered *positive*, the sensitivity of FNA cytology was 72.7%; and if these cases were considered *negative*, the sensitivity of FNA cytology was 25%. (13) The definition of true positives was not available in most of the studies. Note also that most studies used the term *lymphoma* without identifying the subtype.

The specificity of FNA cytology (percentage of cases correctly identified as negative by FNA [true negatives] among all cases identified as negative by excisional biopsy in the study) ranged from 81.2% to 100%.

The use of ancillary techniques such as flow cytometry was evaluated in 2 studies. (2, 9) However, given the small number of patients involved and since the studies were not designed to compare FNA cytology with flow cytometry, it is not possible to compare the 2 techniques.

Two studies reported that FNA cytology identified the correct lymphoma subtype in zero to 68% of the cases, depending on the lymphoma subtype. (4, 8)

Additional details on study results are provided in Table 3.

Length of Time Before Diagnosis by Excisional Biopsy

Three studies evaluated the length of time between the first FNA procedure and the histologic diagnosis of lymphoma by excisional biopsy. (7, 8, 14)

Roh et al (14) reported that the mean time varied between 15 days for the 41 patients whose FNA reports identified a lymphoma, to 49 days for the 19 patients whose reports identified a benign lesion (see Table 3 for additional details). Khillan et al (7) reported a mean of 73 days between the FNA procedure and the diagnosis of lymphoma, with a wide variation from zero to 941 days. (7) No details were provided to explain such a wide variation. Hehn et al (8) reported a mean of > 35 days between an inadequate FNA procedure and the diagnosis of lymphoma from excisional biopsy. (8) See additional details in Table 3.

Risk of Bias Assessment

Appendix 2 provides details of the risk of bias assessment that we conducted on the 9 studies.

One study was considered to have a low risk of bias. (2) The remaining 8 studies (87%) had a moderate to high risk of bias, mainly for the following reasons (note that not all reasons apply to all studies):
- In 6 of the studies, given their retrospective design, the patients had already received both FNA cytology and excisional biopsy, so it is unclear if the decision to perform excisional biopsy was associated with patients' characteristics or with their FNA cytology results.
- It is unclear if the histologic analysis on excisional biopsy was done with or without knowledge of the FNA cytology result.
- The length of time between the FNA cytology and the excisional biopsy was not reported.
- The FNA procedure was not described in detail.
- The lymphoma classification system used was not reported.

Table 1: Observational Studies on Accuracy of FNA Cytology in Diagnosis of Lymphoma—Design and Characteristics

Author, Year Country Lymphoma Type or Site	Study Design	Patient Population	Lymphoma Classification System FNA Procedure	Gold Standard	Time Between FNA and Gold Standard	Outcomes
Karimi-Yazdi et al, 2014 (4) Iran *Head and neck lymphoma*	• Retrospective	• Patients with cervical mass undergoing FNA and excisional biopsy (2006–2010) • N = 47	Not reported Not described	• Histology on excisional or open biopsy • Procedure not described	Not reported	• Sensitivity • Specificity • Number of lymphomas correctly identified
Seningen et al, 2012 (13) United States *Thyroid lymphoma*	• Retrospective	• Patients undergoing thyroid FNA (2001–2007) • Only patients with a subsequent thyroid resection included • N = 25 (lymphoma)	• WHO lymphoma classification system Not described	• Histology on surgical resection sample • Procedure not described	Not reported	• Sensitivity • Specificity
Khillan et al, 2012 (7) United States *Cervical lymphoma*	• Retrospective	• Cervical lymphadenopathy patients who received FNA (1996–2009) & were diagnosed with lymphoma • N = 37	Not reported Not described	• Histology on excisional node biopsy • Procedure not described	• Mean: 73 (range: 0–941) days	• Sensitivity • Time between FNA and lymphoma diagnosis

Author, Year Country Lymphoma Type or Site	Study Design	Patient Population	Lymphoma Classification System FNA Procedure	Gold Standard	Time Between FNA and Gold Standard	Outcomes
Qadri et al, 2012 (1) India *Not site-specific*	• Retrospective	• Patients with generalized lymphadenopathy who received FNA & had excisional node biopsy (2009–2011) • Excluded cases with inadequate samples, poor-quality slides, or incorrect aspiration • N = 123 (lymphoma)	Not reported Not described	• Histology on excisional biopsy • Procedure not described	Not reported	• Sensitivity • Specificity
Ensani et al, 2012 (2) Iran *Non-Hodgkin lymphoma*	• Prospective	• All clinically suspicious cases of non-Hodgkin lymphoma admitted to have surgical (excisional) biopsy (2007–2009) • N = 29	Not reported • FNA in each excised lymph node • 23-gauge needle	• Histology on excisional node biopsy (half lymph node) • Procedure not described	• Concomitant	• Sensitivity • Specificity
Barrena et al, 2011 (9) Spain *Non-Hodgkin lymphoma*	• Prospective	• Consecutive patients who underwent FNA (2002–2007) • N = 161	• WHO lymphoma classification system • FNA collected and assessed by an experienced cytopathologist • 23-gauge needle	• Histology on excisional biopsy or tissue sample • Procedure not described	Not reported	• Sensitivity • Specificity

Author, Year Country Lymphoma Type or Site	Study Design	Patient Population	Lymphoma Classification System FNA Procedure	Gold Standard	Time Between FNA and Gold Standard	Outcomes
Roh et al, 2008 (14) South Korea *Head and neck lymphoma*	• Retrospective	• Patients newly diagnosed with head and neck lymphoma (2000–2005) who underwent FNA and excisional biopsy procedures • N = 109	• REAL, WHO, or Working Formulation[a] classification systems • 23- or 25-gauge needles used • Evaluated by 1 pathologist with > 10 years experience in lymphoma diagnosis	• Histology on excisional biopsy • Procedure not described	• 1–8 weeks[b]	• Number of lymphomas correctly identified • Time between FNA and lymphoma diagnosis
Hehn et al, 2004 (8) United States *Not site-specific*	• Retrospective	• Consecutive patients with FNA and excisional biopsy (1998–2002) with subsequent diagnoses of lymphoma or lymphadenopathy • N = 93	• WHO, REAL, or Working Formulation[a] classifications used • FNA procedure not described • > 70 pathologists interpreted the results	• Histology on excisional biopsy • Procedure not described	• Mean > 35 days • Patients with > 1 year time lag were excluded	• Number of lymphomas correctly identified • Time between FNA and lymphoma diagnosis
Al-Mulhim et al, 2004 (15) Saudi Arabia *Cervical lymphoma*	• Prospective	• Patients with cervical lymphadenopathy for > 3 weeks (2001–2002) • N = 94	Not reported Not described	• Histology on excisional biopsy • Procedure not described	Not reported	• Number of lymphomas correctly identified

Abbreviations: FNA, fine-needle aspiration; N, number; REAL, Revised American-European Classification of Lymphoid Neoplasms; WHO, World Health Organization.
[a]Classification system for non-Hodgkin disease. (14)
[b]Personal communication with the authors.

Table 2: Observational Studies on Accuracy of FNA Cytology in Diagnosis of Lymphoma—Patient Characteristics

Author, Year / Sample Size	Age, years / Sex	Biopsy Sites	History of Malignancies
Karimi-Yazdi et al, 2014 (4) N = 47	• Mean ± SD: 37.4 ± 19.2 • Male: 14 (29.8%)	• Head and neck: 100%	Not reported
Seningen et al, 2012 (13) N = 25	Not reported	• Thyroid: 100%	Not reported
Khillan et al, 2012 (7) N = 37	• Median (range): 49 (26–75) Not reported	• Cervical: 100%	Not reported
Qadri et al, 2012 (1) N = 123	Information specific to lymphoma patients not provided	Not reported	Not reported
Ensani et al, 2012 (2) N = 29	• Mean (range): 63 (10–69) • Male: 15 (51.7%)	• Cervical: 23 (79.3%) • Inguinal: 3 (10.3%) • Axillary: 2 (6.9%) Intraparotid: 1 (3.4%)	• History of lymphoma: 6 (20.7%) • History of other malignancies: 5 (17.2%)
Barrena et al, 2011 (9) N = 400[a]	• Mean (range): 53 (3–92) • Male: 213 (53%)	Not reported	• Initial diagnosis: 312 (80.3%) • Relapse: 77 (19.3%) • Disease progression: 2 (0.5%)
Roh et al, 2008 (14) N = 109	• Mean (range): 52.3 (15–84) Not reported	• Head and neck lymphoma: 100%	**Clinical diagnosis prior to FNA** • Suspected lymphoma: 54 (49.5%) • Non-lymphoma/ metastatic malignancy: 31 (28.4%) • Benign diseases: 24 (22%)
Hehn et al, 2004 (8) N = 93	• Mean (range): 53 (19–94) • Male: 56 (49%)	• Cervical: 44 (41.1%) • Retroperitoneal: 11 (10.3%) • Supraclavicular: 11 (10.3%) • Mediastinum: 6 (5.6%)	Not reported
Al-Mulhim et al, 2004 (15) N = 94	• Mean (range): 30.4 (12–82) • Male: 38 (40.4%)	• Cervical: 100%	Not reported

Abbreviations: FNA, fine-needle aspiration; SD, standard deviation.
[a]As shown elsewhere, the results of this study were based on 161 patients who underwent excisional biopsy; the patient characteristics reported were for the larger cohort of 400 patients.

Table 3: Observational Studies on Accuracy of FNA Cytology in Diagnosis of Lymphoma—Results

Author, Year Sample Size	FNA Samples Considered Inadequate/ Number of FNAs Conducted	FNA Sensitivity (95% CI)	FNA Specificity (95% CI)	% Correct Lymphoma Diagnosis with FNA	Delay of Lymphoma Diagnosis (Time Between FNA and Diagnosis by Excisional Biopsy), days
Karimi-Yazdi et al, 2014 (4) N = 47	Not reported	**Cytology** • Lymphoma: 88% (79–97)	**Cytology** • Lymphoma: 81.2% (70–92)	**Cytology** • Lymphoma sub-classification: 68% • Low grade: 2 (33.3%) • High grade: 8 (88.9%)	Not evaluated
Seningen et al, 2012 (13) N = 25 (lymphoma)	Not reported	**Cytology** • At least suspicious: 72.7% • Positive[a]: 25%	**Cytology** • At least suspicious: 99.6% • Positive: 99.9%	Not evaluated	Not evaluated
Khillan et al, 2012 (7) N = 37	• 2 FNAs: 8 (28.6%) • 3 FNAs: 1 (3.6%) If 1st FNA was not diagnostic	**Cytology** • Lymphoma: 7.1% (0.9–23.5)	Not evaluated	**Cytology** • HL: 0/11	• Mean: 73 (range: 0–941) days • Median: 15 days Due to a non-diagnostic 1st FNA in 7 patients
Qadri et al, 2012 (1) N = 123 (lymphoma)	Not reported	**Cytology** • Lymphoma: 89%	**FNA Cytology** • Lymphoma: 96.2%	Not evaluated	Not evaluated
Ensani et al, 2012 (2) N = 29	• 1 (3.4%) degenerated cells	**Cytology** • NHL: 75% **Flow Cytometry Immunophenotyping** • NHL: 75%	**Cytology** • NHL: 88% **Flow Cytometry Immunophenotyping** • NHL: 94%	**Cytology** • NHL: 9 (75.9%) • HL: 2 (28.6%) • Benign: 2 (33.3%) **Flow Cytometry Immunophenotyping** • NHL: 9 (75%) • HL: 6 (85.7%) • Benign: 5 (83.3%)	Not evaluated
Barrena et al, 2011 (9) N = 161		**FNA Cytology** • HD: 94% • T-cell NHL: 64% • B-cell NHL: 94%	**FNA Cytology** • HD: 100% • T-cell NHL: 100% • B-cell NHL: 100%	Not evaluated	Not evaluated

Author, Year Sample Size	FNA Samples Considered Inadequate/ Number of FNAs Conducted	FNA Sensitivity (95% CI)	FNA Specificity (95% CI)	% Correct Lymphoma Diagnosis with FNA	Delay of Lymphoma Diagnosis (Time Between FNA and Diagnosis by Excisional Biopsy), days
		• Reactive process: 94% **FNA Flow Cytometry** • HD: N/A • T-cell NHL: 92% • B-cell NHL: 96% • Reactive process: 100%	• Reactive process: 94% **FNA Flow Cytometry** • HD: 0 • T-cell NHL: 100% • B-cell NHL: 100% • Reactive process: 96%		
Roh et al, 2008 (14) N = 109	Not reported	**Cytology** • Lymphoma: 58.7% (includes suspected lymphoma)	Not evaluated	**Cytology** • Lymphoma: 41 (37.6%) Not based on subtype[b]	**Time to tissue confirmation of diagnosis after FNA, mean ± SD (days)** **Stratified by the FNA results:** • Lymphoma (n=41): 15 ± 12 • Suspicious (n=23): 25 ±17 • Atypical (n=20): 26 ± 22 • Benign (n=19): 49 ± 78 • Nondiagnostic (n=6): 29 ± 12
Hehn et al, 2004 (8) N = 93	• Non-diagnostic specimens: 13 (14%) • 2 FNAs: most patients	Not evaluated	Not evaluated	**Cytology** • 27 (29%) reported a diagnosis with subtype • Follicular lymphoma: 4 (20%) • DLBCL: 1 (6.3%) • T-lymphomas: 0 **Immunophenotyping** • Follicular lymphoma: 4 (44.4%) • DLBCL: 1 (25%)	• Mean time between inadequate FNA and excisional biopsy diagnosis: > 35 days
Al-Mulhim et al, 2004 (15) N = 94	Not reported	Not evaluated	Not evaluated	**Cytology** • NHL: 12 (86%) • HL: 9 (90%)	Not evaluated

Abbreviations: CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FNA, fine-needle aspiration; HL, Hodgkin lymphoma; N, number; NHL, non-Hodgkin lymphoma; SD, standard deviation.
[a]Suspicious or atypical FNA results considered negative.
[b]Information provided as personal communication.

Conclusions

Based on observational studies, most of which had moderate to high risk of bias, we conclude that:

- fine-needle aspiration cytology alone may not be appropriate in the diagnosis and sub-classification of lymphoma; and
- the use of fine-needle aspiration cytology may be associated with a delay in obtaining a definitive diagnosis of lymphoma.

Acknowledgements

Appendices

Appendix 1: Research Methods

Literature Search Strategy

A literature search was performed on May 28, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process, and all EBM Databases for studies published from January 1, 2004, to May 28, 2014. (Appendix 1 provides details of the search strategies.) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Search Results

Search date: May 28, 2014
Databases searched: Ovid MEDLINE, Ovid MEDLINE In-Process, All EBM Databases (see below)
Limits: 2004-current; English
Filters: none

Databases: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 2014>, EBM Reviews - ACP Journal Club <1991 to May 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2014>, EBM Reviews - Cochrane Central Register of Controlled Trials <April 2014>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <2nd Quarter 2014>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2014>, Ovid MEDLINE(R) <1946 to May Week 2 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 27, 2014>

Search Strategy:

#	Searches	Results
1	exp Lymphoma/	146328
2	(lymphoma* or reticulolymphosarcoma* or germinoblast* or adenolymphoma* or (lymph node* adj2 (tumo?r* or cancer or malignant or neoplas* or carcinoma*))).ti,ab.	141891
3	or/1-2	198540
4	exp Biopsy, Fine-Needle/	9321
5	Biopsy, Needle/	44525
6	((fine needle* adj2 (aspiration* or biops* or cytopathology or cytology)) or FNAC or FNA).mp.	27050
7	or/4-6	61676
8	3 and 7	3771
9	limit 8 to (english language and yr="2004 -Current") [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR; records were retained]	1470
10	Case Reports/	1680066
11	9 not 10	945
12	remove duplicates from 11	930

Appendix 2: Evidence Quality Assessment

Table A1: Risk of Bias Assessment of the Observational Studies According to the QUADAS-2 Tool

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Karimi-Yazdi et al, 2014 (4)	Low risk	High risk[a]	Unclear risk[b]	Unclear risk[c]	Unclear risk[d]	Unclear risk[e]	Unclear risk[f]
Seningen et al, 2012 (13)	High risk[g]	Low risk	Unclear risk[b]	Unclear risk[c]	Unclear risk[d]	Unclear risk[e]	Low risk
Khillan et al, 2012 (7)	High risk[g]	High risk[a]	Unclear risk[b]	Unclear risk[c]	Unclear risk[d]	Unclear risk[e]	Unclear risk[f]
Qadri et al, 2012 (1)	High risk[g]	Low risk	Unclear risk[b]	Unclear risk[c]	Unclear risk[d]	High risk[h]	Unclear risk[f]
Ensani et al, 2012 (2)	Low risk	Unclear[i]	Low risk	Low risk	Low risk	Low risk	Unclear risk[f]
Barrena et al, 2011 (9)	Low risk	Low risk	Low risk	Unclear risk[c]	Unclear risk[d]	Low risk	Low risk
Roh et al, 2008 (14)	High risk[g]	Low risk	Unclear risk[b]	Low risk	Low risk	Low risk	Low risk
Hehn et al, 2004 (8)	Low risk	Low risk	Unclear risk[b]	Low risk	Unclear risk[d]	Unclear risk[e]	Low risk
Al-Mulhim et al, 2004 (15)	Low risk	Low risk	Unclear risk[b]	Unclear risk[c]	Low risk	Unclear risk[e]	Unclear risk[f]

Source (for QUADAS-2 Tool): Whiting et al. (12)

[a]The definition of true positives was not provided, i.e., it is unclear if the correct lymphoma subtype had to be identified by fine-needle aspiration cytology in order for it to be considered a true positive.
[b]Unclear if the results of the excisional biopsy were interpreted without prior knowledge of the fine-needle aspiration cytology. Excisional biopsy was performed after the fine-needle aspiration procedure.
[c]Time interval between fine-needle aspiration and excisional biopsy procedures not reported.
[d]Patients who underwent fine-needle aspiration without undergoing excisional biopsy were excluded from the study as only those who underwent both procedures were included. It is unclear if the decision to perform excisional biopsy on some patients but not others was associated with the patient characteristics or fine-needle aspiration study results.
[e]Fine-needle aspiration procedure not described.
[f]Lymphoma classification system not reported.
[g]Retrospective study, inclusion of consecutive patients not reported.
[h]Cases in which fine-needle aspiration yielded inadequate material and poor quality smears were excluded from the analysis.
[i]Fine-needle aspiration cytology performed on excised lymph node – this may differ from clinical practice.

References

(1)   Qadri SK, Hamdani NH, Shah P, Lone MI, Baba KM. Profile of lymphadenopathy in Kashmir valley: a cytological study. Asia Pac J Cancer Prev. 2012;13(8):3621-5.

(2)   Ensani F, Mehravaran S, Irvanlou G, Aghaipoor M, Vaeli S, Hajati E, et al. Fine-needle aspiration cytology and flow cytometric immunophenotyping in diagnosis and classification of non-Hodgkin lymphoma in comparison to histopathology. Diagn Cytopathol. 2012;40(4):305-10.

(3)   Wakely PE, Jr. The diagnosis of non-Hodgkin lymphoma using fine-needle aspiration cytopathology: a work in progress. Cancer Cytopathol. 2010;118(5):238-43.

(4)   Karimi-Yazdi A, Motiee-Langroudi M, Saedi B, Ensani F, Amali A, Memari F, et al. Diagnostic value of fine-needle aspiration in head and neck lymphoma: a cross-sectional study. Indian J Otolaryngol Head Neck Surg. 2014(Suppl:1):1-80.

(5)   Metzgeroth G, Schneider S, Walz C, Reiter S, Hofmann WK, Marx A, et al. Fine needle aspiration and core needle biopsy in the diagnosis of lymphadenopathy of unknown aetiology. Ann Hematol. 2012;91(9):1477-84.

(6)   Roskell DE, Buley ID. Fine needle aspiration cytology in cancer diagnosis. BMJ. 2004;329(7460):244-5.

(7)   Khillan R, Sidhu G, Axiotis C, Braverman AS. Fine needle aspiration (FNA) cytology for diagnosis of cervical lymphadenopathy. Int J Hematol. 2012;95(3):282-4.

(8)   Hehn ST, Grogan TM, Miller TP. Utility of fine-needle aspiration as a diagnostic technique in lymphoma. J Clin Oncol. 2004;22(15):3046-52.

(9)   Barrena S, Almeida J, Del CG-M, Lopez A, Rasillo A, Sayagues JM, et al. Flow cytometry immunophenotyping of fine-needle aspiration specimens: utility in the diagnosis and classification of non-Hodgkin lymphomas. Histopathology. 2011;58(6):906-18.

(10)   Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008;336(7653):1106-10.

(11)   Reitsma JB, Rutjes AWS, Whiting P, Vlassof VV, Leeflang MMG, Deeks JJ. Assessing Methodological Quality. In: Deeks JJ, Bossuyt PM, Gatsonis C, editors. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1: The Cochrane Collaboration, 2009. Available from http://srdta.cochrane.org/sites/srdta.cochrane.org/files/uploads/ch09_Oct09.pdf 2009.

(12)   Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.

(13)   Seningen JL, Nassar A, Henry MR. Correlation of thyroid nodule fine-needle aspiration cytology with corresponding histology at Mayo Clinic, 2001-2007: an institutional experience of 1,945 cases. Diagn Cytopathol. 2012;40:Suppl-32.

(14)   Roh JL, Lee YW, Kim JM. Clinical utility of fine-needle aspiration for diagnosis of head and neck lymphoma. Eur J Surg Oncol. 2008;34(7):817-21.

(15)   Al-Mulhim AS, Al-Ghamdi AM, Al-Marzooq YM, Hashish HM, Mohammad HA, Ali AM, et al. The role of fine needle aspiration cytology and imprint cytology in cervical lymphadenopathy. Saudi Med J. 2004;25(7):862-5.

About Health Quality Ontario

Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

Based on the evidence provided by Evidence Development and Standards and its partners, the Ontario Health Technology Advisory Committee—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy-makers.

Health Quality Ontario's research is published as part of the *Ontario Health Technology Assessment Series,* which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding Ontario Health Technology Advisory Committee recommendations and other associated reports are also published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

About Health Quality Ontario Publications

To create its CWC reports, the Evidence Development and Standards branch and its research partners review the available scientific literature, making every effort to consider all relevant national and international research and solicit any necessary supplemental information.

In addition, Evidence Development and Standards collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: EvidenceInfo@hqontario.ca
www.hqontario.ca